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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 43/23, 47/575, 65/24, 69/94, 69/712, 235/42, 255/37, 255/54, 255/57, C07D 257/04, 271/06, 271/10, 285/08, 285/10, A61K 31/09, 31 /11, 31 /165, 31 /195, 31 /235, 31 /275, 31 /41

A1

(11) International Publication Number: **WO 95/27692**

(43) International Publication Date: 19 October 1995 (19.10.95)

(21) International Application Number: PCT/US95/04294

(22) International Filing Date: 7 April 1995 (07.04.95)

(30) Priority Data:
08/225,118 8 April 1994 (08.04.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/225,118 (CON)
Filed on 8 April 1994 (08.04.94)

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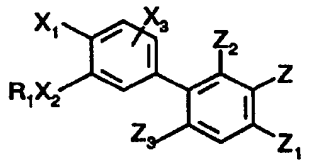
(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: SUBTITUTED BIPHENYL TNF INHIBITORS



(I)

(57) Abstract

Novel compounds for formula (I) are described herein. These compounds inhibit the production of Tumor Necrosis Factor and are useful in the treatment of disease states mediated or exacerbated by TNF production; these compounds are also useful in the mediation or inhibition of enzymatic or catalytic activity of phosphodiesterase IV.

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SUBSTITUTED BIPHENYL TNF INHIBITORS

Field of the Invention

The present invention relates to novel compounds, pharmaceutical compositions containing these compounds, the use of these compounds in treating allergic and inflammatory diseases, and to the use of these compounds to inhibit the production of Tumor Necrosis Factor (TNF).

Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli. Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of the disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all components of chronic bronchial asthma.

An alternative to the "mediator approach" is to regulate the activity of cells responsible for the pathophysiology of asthma. Cyclic AMP (cAMP, adenosine cyclic 3',5'-monophosphate) modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. An elevation of cAMP would produce beneficial effects including: (1) airway smooth muscle relaxation, (2) inhibition of mast cell mediator release, (3) suppression of neutrophil degranulation, (4) inhibition of basophil degranulation, and (5) inhibition of monocyte and macrophage activation. Cyclic AMP has been shown to mediate cellular responses to a wide range of hormones, neurotransmitters and drugs; (Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17-29, 1973).

One potential means to regulate the activity of cells responsible for the pathophysiology of asthma is to control the intracellular levels of cyclic AMP. Cellular cAMP levels are elevated when an appropriate agonist binds to particular cell surface receptors, thereby activating adenylate cyclase to convert Mg^{+2}-ATP to cAMP at an accelerated rate. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (cyclic nucleotide phosphodiesterase hereinafter "PDE"s). Hence, compounds that activate adenylate cyclase or inhibit phosphodiesterase should be effective in suppressing undesirable activation of airway smooth muscle and a wide variety of inflammatory cells.

It has been shown that a distinct PDE isozyme, PDE IV, is responsible for cAMP breakdown in airway smooth muscle and inflammatory cells. (Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd., 1989). Research indicates that inhibition of this

enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. The beneficial effects of PDE IV inhibition are markedly potentiated when the adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids. Thus, PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E_2 and prostacyclin (both activators of adenylate cyclase) are elevated. PDE IV inhibitors offer a unique approach to the pharmacotherapy of bronchial asthma, and possess significant therapeutic advantages over agents currently on the market. The compounds of this invention have the ability to inhibit PDE IV.

The compounds of this invention also inhibit the production of TNF, a serum glycoprotein. Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of undesirable physiological conditions, such as diseases, and including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, human acquired immune deficiency syndrome (AIDS), cachexia secondary to AIDS, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis, in addition to a number of autoimmune diseases, such as multiple sclerosis, autoimmune diabetes and systemic lupus erythematosis.

AIDS results from the infection of T lymphocytes with human immunodeficiency virus (HIV). At least three types or strains of HIV have been identified: HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell-mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into a T lymphocyte requires prior T lymphocyte activation. Once an activated T lymphocyte has been infected with HIV, the T lymphocyte must be maintained in an activated state in order to permit HIV gene expression and/or HIV replication.

Cytokines, including TNF, are implicated in activated T-cell-mediated HIV protein expression and/or virus replication as playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity in an HIV-infected individual, such as by inhibition of TNF production, aids in limiting the maintenance of T cell activation, and thereby mitigates the progression of HIV infection to previously uninfected cells. When HIV infection of previously uninfected cells is diminished, a slowing or elimination of the progression of immune dysfunction caused by HIV infection results.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in the maintenance of HIV infection. These cells, like T cells, are targets

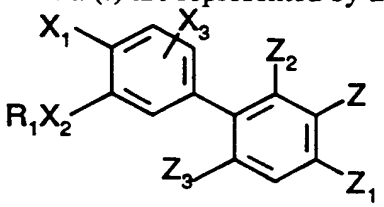
for viral replication, where the level of viral replication is dependent upon the activation state of the cells. (See Rosenberg *et al.*, The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, 1989). Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages (See Poli *et al.*, Proc. Natl. Acad. Sci., 87:782-784, 1990), therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

TNF has also been implicated in various roles with other viral infections, such as that of cytomegalovirus (CMV), influenza virus, adenovirus, and the herpes virus for similar reasons as those noted. TNF is also associated with yeast and fungal infections. Specifically *Candida albicans* has been shown to induce TNF production *in vitro* in human monocytes and natural killer cells. (See Riipi *et al.*, Infection and Immunity, 58(9):2750-54, 1990; and Jafari *et al.*, Journal of Infectious Diseases, 164:389-95, 1991. See also Wasan *et al.*, Antimicrobial Agents and Chemotherapy, 35(10):2046-48, 1990; and Luke *et al.*, Journal of Infectious Diseases, 162:211-214, 1990).

Summary of the Invention

This invention relates to the novel compounds of Formula (I) as shown below, and the pharmaceutically acceptable salts thereof. These compounds are useful in the mediation or inhibition of the enzymatic activity or catalytic activity of PDE IV. These compounds also have TNF inhibitory activity.

The compounds of Formula (I) are represented by the following structure:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is $-(CR_4R_5)_nC(=O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(=O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$ or $-(CR_4R_5)_rR_6$, wherein any alkyl moiety may be optionally substituted with one or more halogens;

R_2 is independently methyl or ethyl, where either methyl or ethyl may be optionally substituted by 1 or more halogens;

each R_4 and each R_5 are independently -H or a C_{1-2} alkyl;

R_6 is -H, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups, one ethyl group or an hydroxyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2: or

b) when R_6 is hydroxyl or -H, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl,or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

each R_7 is independently $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three groups selected from -F, -Br, -Cl, $-NO_2$, $-NR_{10}R_{11}$, $-C(=O)R_8$, $-C(=O)OR_8$, $-OR_8$, -CN, $-C(=O)NR_{10}R_{11}$, $-OC(=O)NR_{10}R_{11}$, $-OC(=O)R_8$, $-NR_{10}C(=O)NR_{10}R_{11}$, $-NR_{10}C(=O)R_{11}$, $-NR_{10}C(=O)OR_9$, $-NR_{10}C(=O)R_{13}$, $-C(=NR_{10})NR_{10}R_{11}$, $-C(=N\text{-}CN)NR_{10}R_{11}$, $-C(=N\text{-}CN)SR_9$, $-NR_{10}C(=N\text{-}CN)NR_{10}R_{11}$, $-NR_{10}S(=O)_2R_9$, $-S(=O)_{m'}R_9$, $-NR_{10}C(=O)C(=O)NR_{10}R_{11}$, $-NR_{10}C(=O)C(=O)R_{10}$, or R_{13};

each R_8 is independently -H or R_9;

each R_9 is independently C_{1-4} alkyl optionally substituted by one to three -F;

each R_{10} is independently $-OR_8$ or R_{11};

each R_{11} is independently -H or C_{1-4} alkyl optionally substituted by one to three -F; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

each R_{12} is independently C_{3-7} cycloalkyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazolyl, 1-imidazolyl, 2-imidazolyl, thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, 2-thienyl, 3-thienyl, 4-thiazolyl, 5-thiazolyl, quinolinyl, naphthyl or phenyl;

each R_{13} is a heterocyclic ring independently selected from oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl or thiadiazolyl, where R_{13} is appended to a compound of Formula (I) through a carbon atom of the heterocyclic ring, and where each heterocyclic ring may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

each R_{14} is independently H or R_7, or when R_{10} and R_{14} are as $NR_{10}R_{14}$, they may together with the nitrogen atom form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

each m is independently 0 to 2;

each m' is independently 0 to 2;

n is 1 to 4;

r is 0 to 6;

each q is independently 0 to 2.

X_1 is YR_6, halogen, nitro, NR_4R_5 or formyl amino;

X_2 is O or NR_8;

X_3 is hydrogen or X_1;

Y is O or $S(=O)_{m'}$;

Y' is O or S;

Z, Z_2 and Z_3 are independently H, $(CH_2)_{1-3}CN$, $(CH_2)_{1-3}(C=O)OR_{14}$, $C(=O)H$, $C(=NR_{10})NR_{10}R_{14}$, $C(=NOR_8)R_{14}$, $C(=O)NR_8NR_8C(=O)R_8$, $C(=O)NR_8NR_{10}R_{14}$, $C(=NOR_{14})R_8$, $C(=NR_8)NR_{10}R_{14}$, $C(=NR_{14})NR_8R_8$, $C(=N\text{-}CN)NR_{10}R_{14}$, $C(=N\text{-}CN)SR_9$, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 4-triazolyl[1,2,3], 5-triazolyl[1,2,3], 3-triazolyl[1,2,4], 5-triazolyl[1,2,4], 5-tetrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-oxadiazolyl[1,2,4], 5-oxadiazolyl[1,2,4], 2-oxadiazolyl[1,3,4], 2-thiadiazolyl[1,3,4], 5-thiadiazolyl[1,2,4], 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolidinyl, 4-oxazolidinyl, 5-oxazolidinyl, 2-thiazolidinyl, 4-thiazolidinyl or 5-thiazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, or 5-imidazolidinyl; wherein all of the heterocyclic ring systems may be optionally substituted one or more times by R_{14};

Z_1 is H, OH, CN, C(=O)OH, $C(=O)OCH_3$ OR $C(=O)NH_2$;

with the provisos that:

a) at least one of Z, Z_2 and Z_3 is other than H;

b) at least one of Z, Z_2 and Z_3 is H; and

c) when Z_1 is -C(=O)OH, then X_2R_1 is not methoxy; and

d) when Z_2 is $(CH_2)_{1-3}CN$, or $(CH_2)_{1-3}C(C=)OR_{14}$, then Z_3 is H.

This invention also relates to pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable excipient.

This invention also relates to pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable excipient.

This invention also relates to a method of mediation or inhibition of the enzymatic activity (or catalytic activity) of PDE IV in mammals, including humans, which comprises administering to a mammal in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method for the treatment of allergic and inflammatory disease which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method for the treatment of asthma which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention further relates to a method of inhibiting TNF production in a mammal, including humans, which comprises administering to a mammal in need of such treatment, an effective TNF inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. This method may be used for the prophylactic treatment or prevention of certain TNF mediated disease states effected thereby.

This invention further relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), which method comprises administering to a human in need of such treatment, an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) are useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF, or will elicit TNF production *in vivo*.

In addition, compounds of Formula (I) are useful in treating yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF, or will elicit TNF production *in vivo*.

Detailed Description of the Preferred Embodiments

DEFINITIONS

As used herein, the following terms and expressions have the indicated meaning.

"Aryl" or "aralkyl", unless specified otherwise, means an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl, or naphthyl. The alkyl chain is meant to include both straight or branched chain radicals of 1 to 4 carbon atoms.

The term "C_{1-2} alkyl", "C_{1-4} alkyl", "C_{1-6} alkyl" or "alkyl groups" includes both straight or branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited thereto, including, but not limited to methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, and the like.

The term "C_{3-7} cycloalkyl" means groups of 3-7 carbon atoms where some or all of them form a ring, such as cyclopropyl, cyclopropylmethyl, cyclopentyl, or cyclohexyl.

"Cytokine" means any secreted polypeptide that affects the functions of cells, and is a molecule which modulates interactions between cells in immune, inflammatory, or hematopoietic responses. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. The cytokine inhibited by the present invention for use in the treatment of an HIV-infected human must be a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication, and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

"Halo" includes all halogen radicals, i.e., chloro, fluoro, bromo, or iodo.

"Heteroaryl" means an aromatic ring system containing one or more heteroatoms, such as imidazolyl, triazolyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, pyrrolyl, furanyl or thienyl.

"Inhibiting the production of IL-1" or "inhibiting the production of TNF" means:

a) a decrease of excessive *in vivo* IL-1 or TNF levels in a human, to normal levels or below normal levels by inhibition of the *in vivo* release of IL-1 by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the translational or transcriptional level, of excessive *in vivo* IL-1 or TNF levels in a human, to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of IL-1 or TNF levels as a postranslational event.

"Percentage" and "%" refers to percentage by weight of a component or ingredient based on the weight of the total composition containing such component or ingredient.

"TNF mediated disease or disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance, is a major component, and whose production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF-ß (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-ß are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

This invention relates to a method for mediating or inhibiting the enzymatic activity or catalytic activity of PDE IV in a mammal in need thereof and for inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

PDE IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases, including: asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of

diabetes insipidus and central nervous system disorders such as depression and multi-infarct dementia.

The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may also be used in association with the veterinary treatment of animals, other than humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis. Additionally, a compound of Formula (I) may be administered in conjunction with other drugs of choice for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymycins, such as Polymycin B; the class of compounds called the imidazoles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole; and the class of compounds called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

A compound of Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of Formula (I) to a mammal in need of such treatment. Preferably, a compound of Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

PREFERRED COMPOUNDS

Preferred compounds of Formula I are as follows:

Preferred R_1 substituents for the compounds of the Formula (I) are C_{4-6} cycloalkyl with or without an hydroxyl group, CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, C_{7-11}

polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C_{1-2} alkyl optionally substituted by 1 or more fluorines, $-(CH_2)_{1-3}C(O)O(CH_2)_{0-2}CH_3$, $-(CH_2)_{1-3}O(CH_2)_{0-2}CH_3$, and $-(CH_2)_{2-4}OH$. When R_1 for the compounds of the Formula (I) is or contains an alkyl moiety substituted by 1 or more halogens, the halogens are preferably fluorine and chlorine. A preferred alkyl moiety substituted by 1 or more halogens is C_{1-4} alkyl substituted by 1 or more fluorines. A more preferred halo-substituted alkyl chain length is one or two carbons, and most preferred are the moieties $-CF_3$, $-CH_2F$, $-CHF_2$, $-CF_2CHF_2$, $-CH_2CF_3$, and $-CH_2CHF_2$

When the R_1 term contains the moiety (CR_4R_5), the R_4 and R_5 terms are independently hydrogen or alkyl. This allows for branching of any individual methylene unit to be independent of branching in any other methylene unit, e.g., $(CR_4R_5)_n$ wherein n is 2 can be $-CH_2CH(-CH_3)-$, for instance. The individual hydrogen atoms of the repeating methylene unit or the branching hydrocarbon can optionally be substituted by fluorine independent of each other to yield, for instance, the preferred R_1 substitutions, as noted above.

When R_1 is a C_{7-11} polycycloalkyl, examples are bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo[5.2.1.$0^{2,6}$]decyl, etc., where additional examples of which are described in Saccamano *et al.*, WO 87/06576, published 5 November 1987, whose disclosure is incorporated herein by reference in its entirety.

Preferred X_1 groups are those wherein X_1 is YR_2 and Y is oxygen. The preferred X_2 group is that wherein X_2 is oxygen. The preferred X_3 group is that wherein X_3 is hydrogen.

Preferred R_2 groups are a C_{1-2} alkyl optionally substituted by 1 or more halogens. The halogen atoms are preferably fluorine and chlorine, more preferably fluorine. More preferred R_2 groups are those wherein R_2 is methyl, or the fluoro-substituted alkyls, specifically a C_{1-2} alkyl, such as a $-CF_3$, $-CHF_2$, or $-CH_2CHF_2$ moiety. Most preferred are the $-CHF_2$ and $-CH_3$ moieties.

Preferred rings when R_{10} and R_{14} are as $-NR_{10}R_{14}$ and together with the nitrogen atom to which they are attached form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 2-triazolyl, 1-tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, and pyrrolyl.

Preferred groups for $-NR_{10}R_{14}$ which contain a heterocyclic ring are 5-(R_{14})-1-tetrazolyl, 2-(R_{14})-1-imidazolyl, 5-(R_{14})-2-tetrazolyl, 4-(R_{14})-1-piperazinyl or 4-(R_{15})-1-piperazinyl.

Preferred rings for R_{13} include (2-, 4- or 5-imidazolyl), (3-, 4-, or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]),

(2,thiadiazolyl[1,3,4]), (2-, 4- or 5-thiazolyl), (2-, 4- or 5-oxazolidinyl), (2-, 4- or 5-thiazolidinyl) or (2-, 4- or 5-imidazolidinyl).

Preferred are those compounds of Formula (I) wherein R_1 is -C_{4-6} cycloalkyl with or without an hydroxyl group, -CH_2-cyclopropyl, -CH_2-C_{5-6} cycloalkyl, tetrahydrofuran-3-yl, (3- or 4-cyclopentenyl), benzyl or -C_{1-2} alkyl optionally substituted by 1 or more fluorines, and -$(CH_2)_{2-4}$ OH; R_2 is methyl or fluoro-substituted alkyl and X_1 is YR_2.

Most preferred are those compounds wherein R_1 is cyclopentyl, 3-hydroxycyclopent-1-yl, -CH_2-cyclopropyl, methyl or CF_2H; X is YR_2; Y is oxygen; X_2 is oxygen; X_3 is hydrogen; and R_2 is CF_2H or methyl.

It will be recognized that some of the compounds of Formula (I) may exist in both racemic and optically active forms; some may also exist in distinct diastereomeric forms possessing distinct physical and biological properties. Furthermore, some of the compounds of Formula (I) may exist in more than one tautomeric form, e.g., imines are a tautomeric form of enamines. All of these compounds are considered to be within the scope of the present invention.

Exemplified compounds of Formula (I) are:

3-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-5-methyl[1,2,4]oxadiazole;

5-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-3-methyl[1,2,4]oxadiazole;

5-(3'-cyclopentyloxy-2,6-difluoro-4'methoxy[1,1']biphenyl-3yl)-3-methyl[1,2,4]oxadiazole;

5-(4-cyano-3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-3-methyl[1,2,4]oxadiazole;

2-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-5-methyl[1,3,4]oxadiazole;

2-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-5-methyl[1,3,4]thiadiazole;

5-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-3-methyl[1,2,4]thiadiazole;

5-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-1-methyl-1H-tetrazole;

5-(3'-cyclopentyloxy-4-'methoxy[1,1']biphenyl-3yl)-2-methyl-2H-tetrazole;

3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-3-acetonitrile;

3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-2-acetonitrile; or

3'-cyclopropylmethoxy-4-hydroxy-4'-methoxy[1,1']biphenyl-3-carboxaldehyde.

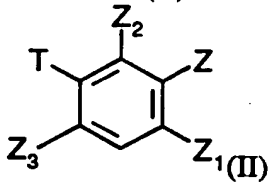
All of the compounds of Formulas (I) are useful in the method of inhibiting the production of TNF, preferably by macrophages, monocytes or macrophages and monocytes, in a mammal, including humans, in need thereof. All of the compounds of Formulas (I) are useful in the method of inhibiting or mediating the enzymatic or catalytic activity of PDE IV and in treatment of disease states mediated thereby.

METHODS OF PREPARATION

Preparation of the compounds of Formula (I) can be carried out by one of skill in the art according to the procedures outlined in the Examples, *infra*. The remaining

compounds of the Formula (I) not described therein may be prepared by the analogous processes disclosed herein which comprise:

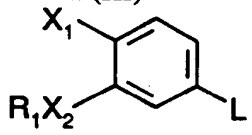
(a) reacting a compound of Formula (II)



(II)

wherein Z, Z_1, Z_2 and Z_3 represents Z, Z_1, Z_2 and Z_3 as defined in relation to Formula (I) or a group convertible to Z,Z_1, Z_2 and Z_3 by standard synthetic methods, and T represents bromo, iodo or trifluoromethylsulfonoxy;

(b) with a compound of Formula (III)



(III)

wherein R_1, X_1 and X_2 represent R_1, X_1 and X_2 respectively, as previously defined in relation to Formula (I) or a group convertible to R_1, X_1 and X_2 respectively, by standard synthetic methods, and L is a metallic group or a group convertible to a metallic group, such as a boronic acid in the presence of a suitable base, a trialkyl tin, a magnesium halide, a lithium cyanocuprate complex, a mercury salt, or a zinc derivative as prepared, for example, by the transmetallation of the corresponding lithium compound with a zinc halide;

(c) in a suitable non-reacting solvent, under a suitable inert atmosphere, and in the presence of a suitable catalyst.

The procedure to react the compounds of Formulas (II) and (III) to form a biphenyl compound of Formula (I), or a biphenyl precursor to a compound of Formula (I), may be referred to as a coupling reaction.

According to a presently preferred method of preparation, aqueous ethylene glycol dimethyl ether, argon and palladium (II) acetate are preferred as the solvent, atmosphere and catalyst, respectively. Boronic acid is a presently preferred L group, and bromo is a presently preferred T group. To form a compound of Formula (I), palladium (II) acetate is dissolved in ethylene glycol dimethyl ether, and the solution is purged of oxygen by bubbling with argon. To the solution is added a compound of Formula (II), a compound of Formula (III), an alkali metal carbonate or bicarbonate such as sodium bicarbonate, and water to facilitate dissolution of the reactants. The mixture is again purged of oxygen by bubbling with argon, and then stirred at a temperature of between about 20 °C and about 100 °C until the reaction is complete. According to a presently preferred procedure, approximately 1.1 moles of a compound of Formula (III) are charged for each mole of a compound of Formula (II). According to a presently preferred procedure, the solvent comprises from about 5% to about 60% water as needed to maximize reactant solubility.

According to a presently preferred procedure, the palladium acetate catalyst is present at about 5 to about 30 molar percent, and the base is present at about 200 to about 300 mole percent, calculated on the moles of a compound of Formula (III).

Another presently preferred procedure for the preparation of compounds of the Formula (I), wherein Z is 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 4-triazolyl[1,2,3], 5-triazolyl[1,2,3], 3-triazolyl[1,2,4], 5-triazolyl[1,2,4], 5-tetrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-oxadiazolyl[1,2,4], 5-oxadiazolyl[1,2,4], 2-oxadiazolyl[1,3,4], 2-thiadiazolyl[1,3,4], 5-thiadiazolyl[1,2,4], 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolidinyl, 4-oxazolidinyl, 5-oxazolidinyl, 2-thiazolidinyl, 4-thiazolidinyl or 5-thiazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, or 5-imidazolidinyl; wherein all of the heterocyclic ring systems may be optionally substituted one or more times by R_{14}, utilizes a palladium catalyst, dissolved in a suitable solvent, having stabilizing ligands where the ligands are chosen from, for example, triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene or 1,4-bisdiphenylphosphinylbutane.

Alternatively the stabilized catalyst is prepared *in situ* from a mixture of a palladium salt, such as the acetate or the bromide, with a stabilizing ligand such as one of the phosphine ligands hereabove exemplified, dissolved in a suitable solvent and the mixture heated in the range of about 50 °C to about 70 °C until the catalyst solution has formed, where exemplary solvents are dimethyl formamide, toluene, tetrahydrofuran or preferably ethylene glycol dimethyl ether. Compounds of Formula (II) and Formula (III) where L is preferably boronic acid are then added together with an appropriate base such as a trialkylamine, or preferably with an alkali metal bicarbonate or carbonate and about 5 to about 25% water to maximize reagent solubility, to the catalyst solution, and the mixture heated under an appropriate atmosphere, for example argon, to provide a compound of Formula (I).

Compounds of Formula (II) wherein Z is 3-methyl[1,2,4]oxadiazole, 5-methyl[1,2,4]oxadiazole, 5-methyl[1,3,4]oxadiazole, or 5-methyl[1,3,4]thiadiazole are prepared by the procedures described in W. Tully, C. Gardener, R. Gillespie, and R. Westwood, J. Medicinal Chem. 34, 2060-2067 (1991), as exemplified herein.

Compounds of Formula (II) wherein Z is 1-alkyl tetrazole are prepared by heating the corresponding N-alkyl carboxamides with thionyl chloride and treating the resulting N-alkyl imidoyl chlorides with sodium azide by the procedure of A. Padwa, et al., J. Org. Chem., 44, 3281-3287 (1979), as exemplified herein.

Compounds of Formula (II) wherein Z is 2-alkyl tetrazole are prepared by alkylation of the unsubstituted tetrazole with an alkyl iodide. The compounds of Formula (II) where Z is an unsubstituted tetrazole are prepared from the corresponding

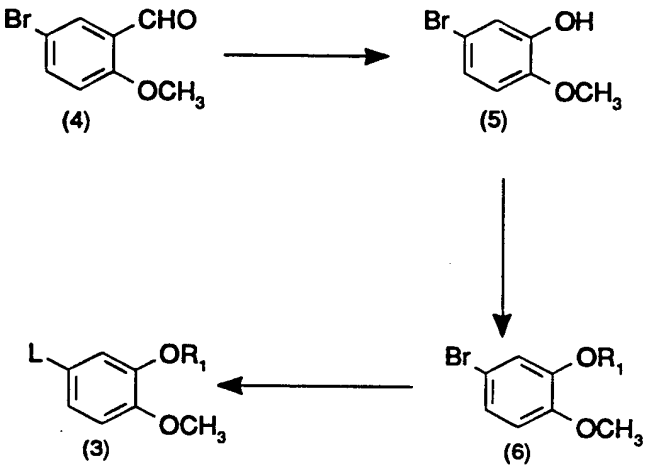
nitriles by the procedure of S.Wittenberger and B. Donner, J. Org. Chem., 58, 4139-4140 (1993), as exemplified herein.

Compounds of Formula (II) wherein Z is 3-alkyl[1,2,4]thiadiazole are prepared by treatment of the corresponding thioamides sequentially with a N,N-dimethylalkylamide, i.e., N,N-dimethylalkaneamide followed by an amino transfer reagent such as hydroxylamine-O-sulfonic acid by the procedure of Y. Lin, S. Lang, Jr., S. Petty, J. Org. Chem., 45, 3750-3753 (1980), as exemplified herein.

Some compounds of Formula (I) may be prepared from other compounds of Formula (I) by, e.g., functional group manipulation of the Z, Z_1, Z_2 or Z_3 group. Additional manipulations of the Z, Z_1, Z_2 or Z_3 groups may be accomplished by the processes described in co-pending U.S. application Serial Number 862,030, filed 2 April 1992 and its corresponding U.S. continuation-in-part application Serial Number 968,762, filed 30 October 1992.

Compounds of Formula (3) may be prepared as illustrated in Scheme 1, and as described in detail in Synthetic Example 1. A brominated anisaldehyde (4) may be reduced to a corresponding hydroxy derivative (5) , and the hydroxy derivative (5) can be converted to a corresponding ether compound of Formula (6), followed by conversion of the bromide to a metallic group L to form a compound of Formula (3).

Scheme I



The following examples are set out to illustrate how to make the compounds of this invention and methods for determining associated therapeutic activity. These examples are not intended to limit the invention in any manner, as their purpose is illustrative rather than limiting.

SYNTHETIC EXAMPLES

Example 1

Preparation of 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxylic acid

1(a) 5-bromo-2-methoxyphenol

To a stirred solution of 5-bromo-*o*-anisaldehyde (Aldrich Chemical Company Inc., 25 g, 116 mmol) in methanol (233 mL) was added cold hydrogen peroxide (30%, 27.7 mL, 244 mmol) followed by concentrated sulfuric acid (5.4 mL, 97 mmol). The reaction mixture was maintained at 70 °C for 6.5 h, stirred at ambient temperature for 72 h and concentrated *in vacuo*. The residue was poured into ice-water and extracted with ethyl ether (three times). The combined organic phase was washed with 3 N hydrochloric acid (twice), water, saturated brine, dried over magnesium sulfate and stripped *in vacuo* to afford an oily orange solid.

1(b) 3-cyclopentyloxy-4-methoxyphenyl bromide

To a stirred solution of 5-bromo-2-methoxyphenol (11.9 g, 58.6 mmol) in dry dimethyl formamide (65 mL) was added cyclopentyl bromide (9.52 mL, 88 mmol) and powdered potassium carbonate (12.15 g, 88 mmol). The reaction mixture was maintained at 70 °C for 2 h, 90 °C for 1 h, and stirred at ambient temperature for 72 h. The volatiles were removed *in vacuo* and the residue partitioned between water and ether. The organic phase was washed with water (three times), saturated brine, dried over anhydrous sodium sulfate and stripped *in vacuo*. The residue was purified by chromatography (silica gel, 33-40% methylene chloride / hexanes) to afford the titled compound as a colorless oil (11.33 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dd, J_1=8.5 Hz, J_2=2.4 Hz) superimposed upon 6.97 (d, J=2.1 Hz) (2H total), 6.72 (d, J=8.4 Hz, 1H, 4.73 (dt, J_1=J_2=6.0 Hz, 1H), 3.82 (s, 3H), 1.96-1.81 (m, 6H), 1.63-1.56 (m, 2H).

1(c) 3-cyclopentyloxy-4-methoxyphenyl-1-boronic acid

To a stirred solution of 3-cyclopentyloxy-4-methoxyphenyl bromide (9.0 g, 33.2 mmol) in dry tetrahydrofuran (105 mL) under an argon atmosphere at -78 °C was added dropwise a 2.58 M solution of *n*-butyl lithium in hexanes (14.6 mL, 36.5 mmol) followed after 2 h stirring by trimethyl borate (4.52 mL, 39.8 mmol). After stirring at ambient temperature for 72 h, the reaction mixture was treated with a solution of 10% aqueous hydrochloric acid (50 mL), stirred for 20 min, and extracted with ethyl acetate three times. The combined organic phase was washed with saturated brine, dried over sodium sulfate (anhydrous) and concentrated *in vacuo*. The residue was purified by chromatography, preabsorbing on silica gel, and removing the impurities with 0-2% methanol in 10% ethyl acetate / methylene chloride. The titled compound was eluted with 5% methanol in ethyl acetate / methylene chloride (1:10) and concentrated *in vacuo* to afford a white solid (5.0 g, 64%). mp 173-174.5 °C.

1(d) 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxylic acid

To dimethoxyethane (6 mL) and water (6 mL), deoxygenated with argon and at room temperature, was added palladium acetate (0.016 g, 0.07 mmol), then, as a mixture of solids, 3-iodobenzoic acid (0.22 g, 0.87 mmol), 3-cyclopentyloxy-4-methoxyphenyl boronic acid (0.23 g, 0.96 mmol) and sodium bicarbonate (0.30 g, 3.5 mmol). The reaction was stirred in the dark under an argon atmosphere for 24 h, then diluted with 5:95 methanol:dichloromethane, washed with 10% hydrochloric acid, water, and brine, was dried ($MgSO_4$), was filtered and was concentrated. The crude mixture was purified by flash chromatography, eluting with 1:9 methanol:dichloromethane, to afford the title compound (0.22 g, 81%), which was further triturated with dichloromethane:hexanes to provide a white solid. mp 146-148 °C. Anal. ($C_{19}H_{20}O_4 \cdot 0.5\ H_2O$) calcd: C, 71.01; H, 6.59; found: C, 70.93; H, 6.35.

Example 2

Preparation of methyl 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxylate

A solution of 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxylic acid (0.15 g, 0.47 mmol) in methanol (5 mL) was treated with chlorotrimethylsilane (0.1 mL, 0.79 mmol), was stirred at room temperature under an argon atmosphere for 3 days and was concentrated. The crude mixture was purified by flash chromatography, eluting with 5:95 ethyl acetate:hexanes, to afford the title product (0.08 g, 53 %), which was further triturated with dichloromethane:hexanes to provide a white solid. mp 84-85 °C. Anal. ($C_{20}H_{22}O_4 \cdot 0.75\ H_2O$) calcd: C, 70.67; H, 6.82; found: C, 70.79 H, 6.45.

Example 3

Preparation of 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxamide

To a solution of 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxylic acid (0.300 g, 0.96 mmol) in dry ethylene glycol dimethyl ether (8 mL) was added N-methyl morpholine (0.13 mL, 1.2 mmol) followed by isobutyl chloroformate (0.14 mL, 1.08 mmol). After 15 min stirring at ambient temperature, ammonium hydroxide (0.6mL, 4.6 mmol) was added dropwise, and the mixture stirred for another 2 h. The reaction mixture was concentrated *in vacuo*, and the residue partitioned between aqueous sodium carbonate solution and methylene chloride. The organic phase was washed with aqueous sodium carbonate solution, dried over anhydrous sodium sulfate, and stripped *in vacuo* to give the titled compound as a tan solid (0.197 g, 66%). mp 134.5-136 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, J=1.7 Hz, 1H), 7.72-7.69 (m, 2H), 7.49 (t, J=7.8 Hz, 1H), 7.16-7.12 (m, 2H), 6.95 (d, J=8.1, 1H), 6.15 (br s, 0.78H), 5.68 (br s, 0.76H), 4.87 (m, J=0.3, 1H), 3.89 (s, 3H), 2.02-1.82 (m, 6H), 1.68-1.58 (m, 7H with H_2O).

Example 4

Preparation of 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-N-methyl carboxamide

Following the procedure of Example 3 except substituting a 40% aqueous solution of methylamine for ammonium hydroxide and purifying the product by chromatography

(silica gel, 1% methanol / chloroform) afforded the title compound as an off-white solid (0.272 g, 52%). mp 112-114 °C; Anal. ($C_{20}H_{23}NO_3 \cdot 1/8\ H_2O$) calcd: C 73.31, H 7.15, N 4.27; found: C 73.26, H 7.13, N 4.33.

Example 5

Preparation of methyl 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-acetate

5(a) 3-bromophenyl acetic acid methyl ester

To a solution of 3-bromophenyl acetic acid (Aldrich Chemical Company, Inc., 0.50 g, 2.33 mmol) in dry methanol (2.5 mL) at ambient temperature was added trimethylsilyl chloride (0.9 mL, 7.0 mmol) dropwise. After stirring for 24 h at ambient temperature, the reaction mixture was heated to reflux for 30 min, and then partitioned between iced 5% sodium carbonate solution and ethyl acetate. The combined organic phase was washed with water, saturated brine, dried over anhydrous sodium sulfate and stripped *in vacuo* to afford an oil.

5(b) methyl 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-acetate

To an argon purged solution of palladium acetate (0.0097 g, 0.043 mmol) dissolved in dry ethylene glycol dimethyl ether (4.8 mL) was added with stirring 3-bromophenyl acetic acid methyl ester (0.103 mL, 0.576 mmol), a powdered mixture of 3-cyclopentyloxy-4-methoxyphenylboronic acid (0.15 g, 0.636 mmol) and sodium bicarbonate (0.118 g, 1.41 mmol) and water (1.5 mL) followed by repurging with argon. The reaction mixture was stirred at ambient temperature for 18 h, then concentrated *in vacuo*. The residue was absorbed onto silica gel and purified by chromatography (silica gel, 5-10% ethyl acetate / hexanes) and dried at 50 °C *in vacuo* to afford the titled compound as white crystals (0.163 g, 83%). mp 59-60.5°C; Anal. ($C_{21}H_{24}O_4$) calcd: C 74.09, H 7.11; found: C 74.20, H 7.20.

Example 6

Preparation of 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-4-carbonitrile Following the procedure of Example 5(b), except substituting 4-bromobenzonitrile (Aldrich Chemical Company, Inc.) for 3-bromophenyl acetic acid methyl ester and recrystallizing from methanol gave the titled compound as white crystals (0.124 g, 73%). mp 97-98.5 °C; Anal. ($C_{19}H_{19}NO_2$) calcd: C 77.79, H 6.53, N 4.77; found: C 77.83, H 6.58, N 4.64.

Example 7

Preparation of 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carbonitrile Following the procedure of Example 5(b), except substituting 3-bromobenzonitrile (Aldrich Chemical Company, Inc.) for 3-bromophenyl acetic acid methyl ester and chromatographing (15-20% ethyl acetate / hexanes) gave the titled compound as white crystals (0.471 g, 76%). mp 66-67.5 °C; Anal. ($C_{19}H_{19}NO_2$) calcd: C 77.79, H 6.53, N 4.77; found: C 77.80, H 6.54, N 5.13.

Example 8

Preparation of methyl 4-cyano-3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxylate

8(a) methyl 2-hydroxy-5-bromobenzoate

A solution of methyl 2-hydroxybenzoate (8.0 g, 52.6 mmol) in acetic acid (200 mL) at room temperature was treated dropwise over 1 h with a solution of bromine (5.15 mL, 100 mmol) in acetic acid (50 mL), stirred for 8 h, was diluted with ether, was washed with aqueous sodium bisulfite, aqueous sodium carbonate, and water, was dried ($MgSO_4$), was filtered and was concentrated to afford the title intermediate as a white solid (11.4 g, 94 %). mp 57- 58 °C.

8(b) methyl 3'-cyclopentyloxy-4-hydroxy-4'-methoxy[1,1']biphenyl-3-carboxylate

The title intermediate was prepared following the procedure of Example 1(d), except substituting methyl 2-hydroxy-5-bromobenzoate for 3-iodobenzoic acid.

8(c) methyl 3'-cyclopentyloxy-4'-methoxy-4-trifluoromethylsulfonato[1,1']biphenyl-3-carboxylate

To methyl 3'-cyclopentyloxy-4-hydroxy-4'-methoxy[1,1']biphenyl-3-carboxylate (0.33 g, 0.59 mmol) in pyridine (3 mL) at 0 °C under an argon atmosphere was added trifluoromethane sulfonic anhydride (0.12 mL, 0.71 mmol). The reaction was stirred at room temperature for 2.5 h, was quenched with 10% hydrochloric acid, was extracted three times with ethyl acetate, was dried ($MgSO_4$), was filtered and was concentrated. The crude mixture was purified by flash chromatography, eluting with 1:9 ethyl acetate:hexanes to afford the title intermediate as a colorless liquid (0.15g, 44%). ^1H NMR (400 MHz, $CDCl_3$) d 8.22 (d, J=2.4 Hz, 1H), 7.75 (dd, J=8.5, 2.4 Hz, 1H), 7.33 (d, J=8.5 Hz, 1H), 7.13 (dd, J= 8.2, 2.1 Hz, 1H), 7.08 (d, J=2.1 Hz, 1H), 6.96 (d, J=8.2 Hz, 1H), 4.87 (m, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 1.8-2.0 (m, 6H), 1.6-1.7 (m, 2H).

8(d) Methyl 4-cyano-3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxylate

A solution of methyl 3'-cyclopentyloxy-4'-methoxy-4-trifluoromethylsulfonato[1,1']biphenyl-3-carboxylate (0.45 g, 0.95 mmol) in deoxygenated dimethylformamide (9.5 mL) was treated with potassium cyanide (0.09 g, 1.43 mmol), palladium acetate (0.032 g, 0.14 mmol), triphenylphosphine (0.075 g, 0.29 mmol) and coarsely ground potassium hydroxide (0.08 g, 1.43 mmol). The reaction was heated at 100-105 °C for 15 min, cooled, diluted with water, and extracted twice with ethyl acetate. The combined organic layers were washed three times with water, with aqueous sodium carbonate and brine, were dried ($MgSO_4$), were filtered and were concentrated. The crude mixture was purified by flash chromatography, eluting with 2:8 ethyl acetate:hexanes to afford the title product as a colorless oil (0.19g, 57 %), which was further triturated with dichloromethane:hexanes to provide a white solid. mp 101-

103 °C; Anal. ($C_{21}H_{21}NO_4 \cdot 0.125\ H_2O$) calcd: C, 71.32; H, 6.06; N, 3.96; found: C, 71.32; H, 6.03; N, 3.87.

Example 9

Preparation of 3'-cyclopentyloxy-2,6-difluoro-4'-methoxy[1,1']biphenyl-3-carboxylic acid

9(a) 2,4-difluoro-3-iodobenzoic acid

A solution of di-isopropylamine (1.55 mL, 11.1 mmol) in tetrahydrofuran (15 mL) at 0 °C under an argon atmosphere was treated with 2.5 M *n*-butyllithium in hexanes (4.20 mL, 10.5 mmol), stirred for 30 min, and cooled to -78 °C. A solution of 2,4-difluorobenzoic acid (0.79 g, 5.0 mmol) in tetrahydrofuran (8 mL) was added over 15 min, followed after 30 min by the addition of a solution of iodine (1.4 g, 5.5 mmol) in tetrahydrofuran over 15 min. After 30 min the reaction was quenched with 1 N hydrochloric acid, warmed to room temperature, extracted three times with 5:95 methanol:dichloromethane, dried ($MgSO_4$), filtered, and concentrated. Recrystallization from dichloromethane:hexanes provided the title intermediate as a white solid (1.15 g, 81%). mp 206-208 °C.

9(b) 3'-cyclopentyloxy-2,6-difluoro-4'-methoxy[1,1']biphenyl-3-carboxylic acid

To dimethoxyethane (5 mL) and water (5 mL), deoxygenated with argon and at room temperature, was added palladium acetate (0.013 g, 0.06 mmol), then as a mixture of solids 2,4-difluoro-3-iodobenzoic acid (0.20 g, 0.72 mmol), 3-cyclopentyloxy-4-methoxyphenyl boronic acid (0.19 g, 0.79 mmol) and sodium carbonate (0.24 g, 2.3 mmol). The reaction was stirred in the dark under an argon atmosphere for 24 h, then diluted with 5:95 methanol:dichloromethane, washed with 10% hydrochloric acid, water and brine, dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by flash chromatography, eluting with 0.2:2:98 acetic acid:methanol:dichloromethane to afford the title compound as a white solid (0.17 g, 67%). mp 154-155 °C. Anal. ($C_{19}H_{20}O_4$) calcd: C, 65.51; H, 5.21; found: C, 65.11; H, 5.20.

Example 10

Preparation of methyl 3'-cyclopentyloxy-2,6-difluoro-4'-methoxy[1,1']biphenyl-3-carboxylate

A solution of 3'-cyclopentyloxy-2,6-difluoro-4'-methoxy[1,1']biphenyl-3-carboxylic acid (0.15 g, 0.42 mmol) in methanol (2.5 mL) was treated with chlorotrimethylsilane (0.16 mL, 1.26 mmol) and stirred at room temperature under an argon atmosphere for 48 h. The reaction was diluted with water, extracted three times with dichloromethane, dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by flash chromatography, eluting with 1:9 ethyl acetate:hexanes to afford the title compound as a colorless oil (0.13 g, 84%) which turned gummy with time.

Anal. ($C_{20}H_{20}F_2O_4 \cdot 0.5\ H_2O$.) calcd: C, 64.68; H, 5.70; found: C, 64.51; H, 5.44. ^1H NMR (400 MHz, $CDCl_3$) δ 7.9-8.0 (m, 1H), 6.9-7.1 (m, 4H), 4.78 (m, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 1.8-2.0 (m, 6H), 1.6-1.7 (m, 2H).

Example 11

Preparation of 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3,4-dicarbonitrile

11(a) 4-bromophthalic anhydride

Crystalline 4-bromophthalic acid (Aldrich) was distilled at atmospheric pressure, collecting the material of bp >290 °C, drying *in vacuo* and grinding to afford the titled compound as a white powder (5.8 g, 78%). mp 100-104 °C.

11(b) 4-bromophthalimide

A powdered mixture of 4-bromophthalic anhydride (5.7 g, 25.1 mmol) and urea (1.51 g, 25.1 mmol) was heated to melting under argon atmosphere and maintained at 150 °C for 10 minutes after gas evolution terminated. The solid obtained on cooling was heated in glacial acetic acid, cooled, filtered, washed with cold water and dried *in vacuo* to afford the titled compound (5.03 g, 89%). mp 228-230 °C (Waldman in J. fur Practische Chemie, 126, 65 (1930) reports mp 229.5 °C).

11(c) 4-bromophthalamide

A rapidly stirred suspension of 4-bromophthalimide (2.5 g, 11.06 mmol) in concentrated ammonium hydroxide (75 mL) was gently heated to dissolve. The mixture was then chilled with the formation of a white precipitate. The chilled mixture was filtered, washed with cold water and the white solid dried *in vacuo* to afford the titled compound (2.08 g, 77%) as a white powder which partially melts at 197 °C, evolves a gas and changes to crystals which melt at 227-229 °C.

11(d) 4-bromo-2-cyanobenzonitrile

A stirred mixture of 4-bromophthalamide (0.400 g, 1.65 mmol) in dry tetrahydrofuran (4.0 mL) under an argon atmosphere was treated sequentially at 0 °C with dry pyridine (1.15 mL, 14.3 mmol) and then, over 0.5 h, dropwise with trifluoroacetic acid anhydride (1.01 mL, 7.14 mmol). After 3 h stirring at ambient temperature, the reaction mixture was added to ice water and partitioned between methylene chloride and water. The organic extract was washed with water, brine dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography (silica; 15-20% ethyl acetate/hexanes) to afford the titled compound as a white solid (0.30 g 88%). mp 138.5-140 °C.

11(e) 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3,4-dicarbonitrile

Following the procedure of Example 5(b), except substituting 4-bromo-2-cyanobenzonitrile for 3-bromophenyl acetic acid methyl ester, employing 5 rather than 24 percent of water (v/v) in the solvent, and heating the reaction mixture at 55 °C for an additional 2 h resulted in only about 75% consumption of the bromide by thin layer chromatography (silica; 1:3; ethyl acetate /hexanes). Another 25% of 3-cyclopentyloxy-

4-methoxyphenylboronic acid (0.0375 g, 0.159 mmol), palladium acetate (0.0025 g, 0.011 mmol), and sodium carbonate (0.049 g, 0.46 mmol) was then added, stirring at ambient temperature for an additional 72 h followed by heating for 3 h at 60 °C. The reaction mixture was concentrated *in vacuo*, partitioned between methylene chloride / water, and the organic phase washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography (silica; hexanes/methylene chloride; 1:2 containing 2-4% ethyl acetate) followed by recrystallization (ethyl acetate/petroleum ether) and drying at 130 °C *in vacuo* to afford the titled compound as a white solid . mp 157.5-159 °C; Anal. ($C_{20}H_{18}N_2O_2 \cdot 1/8$ H_2O) calcd: C 74.94, H 5.74, N 8.74; found (two measurements were made): C 74.92, 75.00, H 5.62, 5.60, N 8.58, 8.56; MS:(CI, NH_3) $[M+NH_4]^+$ 336.1, and $[M+H-C_5H_8]^+$ 250.0.

Example 12

Preparation of 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-3-carboxylic acid12(a) 3-cyclopropylmethoxy-4-methoxyphenyl bromide

Following the procedure of Example 1(b), except substituting cyclopropylmethyl bromide for cyclopentyl bromide, maintaining the reaction mixture at 70 °C for 3 h followed by ambient temperature for 72 h and purifying by chromatography (silica gel, 33-50% methylene chloride/hexanes) gave the titled compound as a white solid (11.5 g, 76%). mp 53-54 °C.

12(b) 3-cyclopropylmethoxy-4-methoxyphenyl-1-boronic acid

Following the procedure of Example 1(c), except substituting 3-cyclopropylmethoxy-4-methoxyphenyl bromide for 3-cyclopentyloxy-4-methoxyphenyl bromide, and purifying by chromatography (silica gel, 2-5% methanol/methylene chloride) gave the titled compound as a white solid (1.74 g, 50%). mp 205-206 °C.

12(c) 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-3-carboxylic acid

Following the procedure of Example 1(d), except utilizing a 50:50 solution of water:ethylene glycol dimethyl ether, substituting 3-cyclopropylmethoxy-4-methoxyphenyl-1-boronic acid for 3-cyclopentyloxy-4-methoxyphenyl-1-boronic acid, substituting ethyl ether for ethyl acetate as the extraction solvent and crystallizing from ethyl ether and drying following chromatography gave the titled compound as white crystals (0.131 g, 72%). mp 147-148 °C; Anal. ($C_{18}H_{18}O_4$) calcd: C 72.47, H 6.08; found: C 72.18, H 6.12.

Example 13

Preparation of 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-3-carboxamide

Following the procedure of Example 3, except substituting 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-3-carboxylic acid for 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxylic acid, purifying the dried, and stripped residue by chromatography (silica gel, 5% methanol / toluene) and crystallizing from ethyl ether gave the titled compound as a

white powder (0.046 g, 60%). mp 148-150 °C; Anal. ($C_{18}H_{19}NO_3$) calcd: C 72.71, H 6.44, N 4.71; found: C 72.54, H 6.43, N 4.49.

Example 14

Preparation of 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-3-carbonitrile

To a stirred mixture of 3'-cyclopropylmethoxy-4'-methoxyphenyl-1-boronic acid (0.20 g, 0.90 mmol), 3-bromobenzonitrile (0.149 g, 0.82 mmol), and tetrakis-triphenylphosphinyl palladium (0.047 g, 0.041 mmol) in dimethylformamide (6 mL) under argon was added triethylamine (0.354 mL, 2.54 mmol). The reaction mixture was purged with argon bubbling, heated at 90-100 °C for 7 h and then partitioned between methylene chloride and dilute aqueous hydrochloric acid. The organic phase was washed with water, dilute aqueous sodium carbonate solution, water, saturated brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 60-80% methylene chloride/hexanes), recrystallized from methanol and dried *in vacuo* to afford the titled compound as white crystals (0.067 g, 29%). mp 101-102 °C; Anal. ($C_{18}H_{17}NO_2$) calcd: C 77.40, H 6.13, N 5.01; found: C 77.30, H 6.11, N 4.96.

Example 15

Preparation of 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-3-acetonitrile

Following the procedure of Example 14, except substituting 3-bromophenylacetonitrile (Aldrich Chemical Company, Inc.) for 3-bromobenzonitrile, chromatographing (silica gel, 80-100% methylene chloride/hexanes) and recrystallizing from ethyl ether gave the titled compound as a white powder (0.041 g, 25%). mp 75-76 °C; Anal. ($C_{19}H_{19}NO_2 \cdot 1/10\ H_2O$) calcd: C 77.32, H 6.56, N 4.75; found (measured twice): C 77.34, 77.38, H 6.47, 6.52, N 4.65, 4.58.

Example 16

Preparation of 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-2-acetonitrile

Following the procedure of Example 14, except substituting 2-bromophenylacetonitrile (Aldrich Chemical Company, Inc.) for 3-bromobenzonitrile, and evaporating the solvent *in vacuo* from the fractions collected from the chromatography, rather than recrystallizing from methanol, gave the titled compound as a resin (0.054 g, 33%). Anal. ($C_{19}H_{19}NO_2 \cdot 1/10\ H_2O$) calcd: C 77.32, H 6.56, N 4.75; found: C 77.36, H 6.59, N 4.51. MS (CI/NH_3) *m/e* 311 $[M+NH3]^+$, 294 $[M+H]^+$.

Example 17

Preparation of methyl 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-3-carboxylate

Following the procedure of Example 14, except substituting methyl 3-iodobenzoate for 3-bromobenzonitrile, and following a first chromatography (silica gel, 40-60% methylene chloride / hexanes) with a second chromatography in which the impure titled compound was preabsorbed onto silica gel (silica gel, 15-20% ethyl acetate / hexanes), and

recrystallizing from ethyl ether gave the titled compound as a white powder (0.057 g, 32%). mp 71-72.5 °C; Anal. ($C_{19}H_{20}O_4$) calcd: C 73.06, H 6.45; found: C 73.02, H 6.54.

Example 18

Preparation of 3'-cyclopropylmethoxy-4-hydroxy-4'-methoxy[1,1']biphenyl

Following the procedure of Example 12(c), except substituting 4-iodophenol (Aldrich Chemical Company, Inc.) for 3-iodobenzoic acid, chromatographing (silica gel, 1% methanol/methylene chloride) and crystallizing from ethyl ether gave the titled compound as white crystals (0.083 g, 63%). mp 117.5-118.5 °C; Anal. ($C_{17}H_{18}O_3$) calcd: C 75.53, H 6.71; found: C 75.45, H 6.76.

Example 19

Preparation of 3'-cyclopropylmethoxy-4-hydroxy-4'-methoxy[1,1']biphenyl-3-carboxaldehyde Following the procedure of Example 18, except substituting 5-bromo-2-hydroxybenzaldehyde (Aldrich Chemical Company, Inc.) for 4-iodophenol, chromatographing twice (silica, 50 to 80% methylene chloride:hexane; silica, 0 to 1% methanol:toluene) and crystallizing from methylene chloride:ethyl ether gave the titled compound as a white crystals (0.047 g, 32%). mp 85-86 °C; Anal. ($C_{18}H_{18}O_4$) calcd: C 72.47, H 6.08; found: C 72.27, H 6.03.

Example 20

Preparation of methyl 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-4-carboxylate

To a stirred solution of 3'-cyclopropylmethoxy-4'-methoxyphenyl-1-boronic acid (0.81 g, 3.65 mmol) dissolved in aqueous (13.6 mL) sodium bicarbonate (0.605 g, 7.20 mmol), under an argon atmosphere ,was added tetrakis-triphenylphosphinyl palladium (0.126 g, 0.109 mmol) and a solution of methyl 4-bromobenzoate (0.774 g, 3.60 mmol) in toluene (8 mL). The suspension was heated at 70 °C for 22 h, cooled and partitioned between methylene chloride and a solution of 5% sodium carbonate also containing concentrated ammonium hydroxide. The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 1:1:8 ethyl acetate:toluene:hexanes) to afford the titled compound as a white solid (0.210 g, 17%). mp 138 °C; Anal. ($C_{19}H_{20}O_4 \cdot 1/8\ H_2O$) calcd: C 72.54, H 6.49; found: C 72.77, H 6.45.

Example 21

Preparation of 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-4-carboxylic acid

To a stirred suspension of 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-4-carboxylic acid methyl ester (0.150 g, 0.48 mmol) in methanol (4.8 mL) was added a solution of potassium hydroxide (0.081 g, 1.44 mmol) in water (2.8 mL) and tetrahydrofuran (0.5 mL). After 6 days, sufficient tetrahydrofuran was added to give a homogeneous reaction mixture. After stirring another 2 days, the reaction was poured into

aqueous dilute hydrochloric acid, extracted (4 times) with chloroform containing a trace of methanol, dried over magnesium sulfate and concentrated *in vacuo*. Trituration with methylene chloride/ethyl ether afforded the titled compound as a solid (0.10 g, 70%). mp 212 °C; Anal. ($C_{18}H_{18}O_4 \cdot 1/4\ H_2O$) calcd: C 71.39, H 6.16; found: C 71.60, H 6.04.

Example 22

Preparation of 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-4-carboxamide

Following the procedure of Example 3, except substituting 3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-4-carboxylic acid for 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxylic acid, and triturating from methylene chloride/ethyl ether gave the titled compound as a white solid (0.040 g, 79%). mp 200-201 °C; Anal. ($C_{18}H_{19}NO_3 \cdot 1/2\ H_2O$) calcd: C 70.57, H 6.58, N 4.57; found: C 70.46, H 6.19, N 4.45.

Example 23

Preparation of 5-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole

A solution of 3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-carboxamide (0.171 g, 0.55 mmol) prepared as described in Example 3 in dimethylacetamide dimethyl acetal (1.7 mL, 10.5 mmol) was heated at 100 °C in a sealed tube for 1 h. The resulting mixture was concentrated *in vacuo* . The residue was dissolved in dioxane (2.0 mL), treated with hydroxylamine hydrochloride (0.54 mg, 0.77 mmol), acetic acid (2.0 mL), 2 M aqueous sodium hydroxide (0.475 mL, 0.95 mmol) and heated at 90 °C in a sealed tube for 2 h. The reaction mixture was cooled, poured into cold water, made alkaline with aqueous sodium carbonate, and extracted four times with ethyl acetate. The organic extract was washed with water, brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was triturated with ethyl ether and recrystallized twice from methanol to give the titled compound as a white solid (0.131 g, 68%). mp 101.5-102.5 °C; Anal. ($C_{21}H_{22}N_2O_3$) calcd: C 71.98, H 6.33, N 7.99; found: C 71.80, H 6.26, N 7.92.

Example 24

Preparation of 3-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-5-methyl[1,2,4]oxadiazole

24(a) 3-bromo-N-hydroxybenzamidine

To a stirred mixture of 3-bromobenzonitrile (0.80 g, 4.4 mmol), hydroxylamine hydrochloride (0.458 g, 6.59 mmol) and pulverized potassium hydroxide (0.37 g, 6.60 mmol) in a pyrex tube under an argon atmosphere was added absolute ethanol (12 mL) and the suspension was sealed and heated at 75 °C for 14 h. After cooling, the reaction mixture was concentrated *in vacuo* and the residue partitioned between methylene chloride and water containing dilute sodium carbonate. The organic phase was washed with saturated brine, dried over sodium sulfate, stripped *in vacuo* to afford white crystals (0.72g, 77%). mp 117-124 °C.

24(b) 3-(3-bromophenyl)-5-methyl[1,2,4]oxadiazole

A solution of 3-bromo-N-hydroxybenzamidine (0.71 g, 3.3 mmol) in dimethylacetamide dimethyl acetal (10 mL of 90% solution in methanol) was heated at 100 °C for 1 h and stripped *in vacuo*. The residue, preabsorbed onto silica (5 mL), was purified by chromatography (silica gel, 2.5% ethyl acetate/hexanes) and concentrated *in vacuo* to afford white crystals (0.65 g, 82%). mp 80-81 °C.

24(c) 3-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-5-methyl[1,2,4]oxadiazole

A solution of palladium acetate (0.013 g, 0.059 mmol) and bis(diphenylphosphino)butane (0.028 g, 0.065 mmol) in ethylene glycol dimethylether (7 mL) was heated for 1 min at 60 °C with argon bubbling, cooled, and treated with a powdered mixture of 3-cyclopentyloxy-4-methoxyphenylboronic acid (0.20 g, 0.847 mmol), 3-(3-bromophenyl)-5-methyl[1,2,4]oxadiazole (0.188 g, 0.788 mmol) and sodium bicarbonate (0.213 g, 2.54 mmol) followed by addition of water (0.27 mL) and repurged with argon bubbling. This mixture was sealed in a pressure tube and heated for 7 h at 100 °C. The reaction mixture was cooled, concentrated *in vacuo*, the residue partitioned in methylene chloride vs water, the organic phase washed with saturated brine and dried over anhydrous potassium carbonate. The mixture was deposited onto silica gel and purified by chromatography (silica gel, 10% ethyl acetate/hexanes), crystallized from ethyl ether and dried *in vacuo* to afford a white powder (0.172 g, 62%). mp 67-70 °C; Anal. ($C_{21}H_{22}N_2O_3$) calcd: C 71.98, H 6.33, N 7.99; found: C 72.04, H 6.47, N 7.73.

Example 25

Preparation of 5-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-1-methyl-1H-tetrazole

25(a) 3-bromo-N-methylbenzamide

To an-ice cold stirred suspension of 40% aqueous methylamine (4 mL) and methylene chloride (4 mL, 52 mmol) was added dropwise 3-bromobenzoyl chloride (0.50 mL, 3.79 mmol). After 10 min, the suspension was partitioned between cold water and methylene chloride and the combined organic layers were washed successively with water, dilute aqueous acetic acid, dilute aqueous sodium carbonate, water and saturated brine. The solvent was removed *in vacuo* to afford a white solid (0.726 g, 90%). mp 91-92 °C.

25(b) 5-(3-bromophenyl)-1-methyl-1H-tetrazole

A solution of 3-bromo-N-methylbenzamide (0.305 g, 1.42 mmol) in thionyl chloride (1.2 mL, 16.4 mmol) was refluxed for 40 min under argon and the excess thionyl chloride removed *in vacuo*. A solution of the residue dissolved in dimethyl formamide (3 mL) was added dropwise to a stirred suspension of sodium azide (0.277 g, 4.3 mmol) in dimethyl formamide at 0 °C and the mixture was maintained at this temperature for 16 h. The reaction mixture was poured into ice-water, made alkaline with 5% aqueous sodium carbonate and extracted (3 times) with ethyl acetate. The combined organic layer was washed with water (3 times), saturated brine, dried over

sodium sulfate (anhydrous) and stripped *in vacuo* to afford a white crystalline solid (0.323 g, 95%). mp 107-108 °C.

25(c) 5-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-1-methyl-1H-tetrazole

Following the procedure of Example 24(c), except substituting 5-(3-bromophenyl)-1-methyl-1H-tetrazole for 3-(3-bromophenyl)-5-methyl[1,2,4]oxadiazole and eluting with ethyl acetate:chloroform (2:98) gave the titled compound as white crystals (0.188 g, 57%). mp 120-121 °C; Anal. ($C_{20}H_{21}N_4O_2 \cdot 4/10\ H_2O$) calcd: C 67.17, H 6.43, N 15.67; found: C 67.18, H 6.32, N 15.60

Example 26

Preparation of 5-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-2-methyl-2H-tetrazole

26(a) 5-(3-bromophenyl)-1H-tetrazole

A mixture of 3-bromo-benzonitrile (0.546 g, 3.00 mmol), dry toluene (6 mL), azidotrimethylsilane (0.796 mL, 6.00 mmol), and dibutyltin oxide (0.0136 g, 0.055 mmol) was stirred at 90 °C for four days in a sealed tube. The reaction mixture was cooled and then concentrated *in vacuo* and treated twice with methanol, followed each time by reconcentration. The residue was partitioned between ethyl acetate and sodium carbonate solution (5%). The organic phase was extracted with an additional portion of sodium carbonate solution, and the combined aqueous phase was acidified with 6N HCl and extracted with ethyl acetate. The organic extract was dried (sodium sulfate) and concentrated *in vacuo* to afford the titled compound as a pale yellow solid (0.597 g, 88%). mp 150-151 °C.

26(b) 5-(3-bromophenyl)-2-methyl-2H-tetrazole

A stirred solution of 5-(3-bromophenyl)-1H-tetrazole (0.4 g, 1.78 mmol) in acetone (3.2 mL) was treated with pulverized potassium hydroxide (0.15 g, 2.67 mmol), water (0.72 mL), and iodomethane (0.166 mL, 2.67 mmol), sealed under argon and stirred for 72 h at ambient temperature. The reaction mixture was poured into ice-water, extracted with methylene chloride (three times), and the combined organic phase washed with water, dried (sodium sulfate) and concentrated *in vacuo*. The residue, a mixture of 5-(3-bromophenyl)-1-methyl-2H-tetrazole and 5-(3-bromophenyl)-2-methyl-2H-tetrazole, was purified by chromatography (silica gel, 50% methylene chloride/hexanes), eluting the titled compound as the faster isomer, a white solid (0.327 g, 77%). mp 93-94.5 °C.

26(c) 5-(3'-cyclopentyloxy-4'methoxy[1,1']biphenyl-3-yl)-2-methyl-2H-tetrazole

Following the procedure of Example 25(c), except substituting 5-(3-bromophenyl)-2-methyl-2H-tetrazole for 3-(3-bromophenyl)-5-methyl[1,2,4]oxadiazole and sodium carbonate for sodium bicarbonate, heating the mixture for 16 h at 85 °C followed by 4 h at 90 °C, washing the organic extract with 5% aqueous sodium carbonate solution, water and saturated brine, and purifying by chromatography (silica gel, 100:0 to 98:2 methylene chloride:ethyl acetate) afforded the titled compound as a

white powder (0.158 g, 67%). mp 105-106 °C; Anal. ($C_{20}H_{22}N_4O_2$) calcd: C 68.55, H 6.33, N 15.99; found: C 68.39, H 6.41, N 15.94.

Example 27

Preparation of 2-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-5-methyl[1,3,4]oxadiazole

27(a) 3-bromobenzoyl-N'-acetyl hydrazine

A stirred mixture of 3-bromobenzoyl hydrazine (2.0 g, 9.3 mmol) in absolute ethanol (20 mL) was treated with triethylamine (2.0 mL, 14.3 mmol) followed by acetic anhydride (1.35 mL, 14.0 mmol) and the resulting solution was refluxed for 2 h. The mixture was allowed to cool, and then water was added to the cooled solution resulting in the precipitation of a white solid. The white solid was isolated by filtration, then washed with water and dried *in vacuo* to afford the titled compound as a mixture of rotational isomers (2.3 g, 96%). mp 151-170 °C.

27(b) 2-(3-bromophenyl)-5-methyl[1,3,4]oxadiazole

A stirred mixture of 3-bromobenzoyl-N'-acetyl hydrazine (0.5 g, 1.94 mmol), phosphorus oxychloride (2.0 mL, 21.4 mmol), and toluene (15 mL) was refluxed for 1.5 h under an argon atmosphere. The cooled mixture was partitioned between chloroform and water, and the organic phase was washed with aqueous 5% sodium carbonate solution (twice), and water, then dried over sodium sulfate. After filtering, the organic phase was concentrated in vacuo, and the residue purified by chromatography (silica, 2 to 5% ethyl acetate/methylene chloride) to afford the titled compound as cream colored crystals (0.35 g, 76%). mp 76-77.5 °C.

27(c) 2-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-5-methyl[1,3,4]oxadiazole

Following the procedure of Example 24(c), except substituting 2-(3-bromophenyl)-5-methyl[1,3,4]oxadiazole for 3-(3-bromophenyl)-5-methyl[1,2,4]oxadiazole, heating the mixture for 10 h at 100 °C, washing the organic extract with 5% aqueous sodium carbonate solution, drying over sodium sulfate, purifying by chromatography (silica gel, 35 to 40% ethyl acetate/hexanes), and crystallizing from ethyl ether gave the titled compound as a white solid containing traces of solvents (mp 111.5-113 °C) which was melted *in vacuo* to afford a cream colored glass (0.127 g, 53%). Anal. ($C_{21}H_{22}N_2O_3 \cdot 1/8\ H_2O$) calcd: C 71.52, H 6.36, N 7.94; found (measured twice): C 71.55, 71.51, H 6.31, 6.28, N 7.86, 7.78; MS: (CI, NH_3) $[M+NH_4]^+$ 368.2, $[M+H]^+$ 351.2, $[M+H\text{-}CH3CN]^+$ 311.2.

Example 28

Preparation of 2-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-5-methyl[1,3,4]thiadiazole

28(a) 2-(3-bromophenyl)-5-methyl[1,3,4]thiadiazole

A stirred mixture of 3-bromobenzoyl-N'-acetyl hydrazine (0.5 g, 1.94 mmol), prepared as described in Example 28(a) above, toluene (19 mL) and Lawessons's reagent (1.0 g, 2.47 mmol) was refluxed for 1.5 h under an argon atmosphere. The cooled mixture was diluted with chloroform (10 mL), basified with a 5% sodium carbonate solution, and

the organic phase washed with water dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography (silica, 2 to 3% ethyl acetate/methylene chloride) to afford the titled compound as a white solid (0.349 g, 70%). mp 63-64.5 °C.

28(b) 2-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-5-methyl[1,3,4]thiadiazole

Following the procedure of Example 24(c), except substituting 2-(3-bromophenyl)-5-methyl[1,3,4]thiadiazole for 3-(3-bromophenyl)-5-methyl[1,2,4]oxadiazole and sodium carbonate for sodium bicarbonate, heating the mixture for 12 h at 100 °C, filtering an ethyl acetate solution of the reaction mixture through Celite, purifying the residue by chromatography (silica gel, 30 to 40% ethyl acetate/hexanes), and crystallizing from ethyl ether gave the titled compound as a white solid (0.127 g, 50%). mp 109.5-110.5 °C; Anal. ($C_{21}H_{22}N_2O_2S$) calcd: C 68.82, H 6.05, N 7.64; found: C 68.80, H 6.05, N 7.56.

Example 29

Preparation of 5-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-3-methyl[1,2,4]thiadiazole

29(a) 3-bromothiobenzamide

A solution of 3-bromobenzonitrile (1.02 g, 5.5 mmol), methanol (50 mL) and 24% aqueous ammonium sulfide (30 mL) was heated at 65-70 °C in a sealed pressure vessel for 1 h, then was purged with argon. After diluting with cold water, the mixture was extracted three times with dichloromethane, the combined extracts were washed twice with water, were dried ($MgSO_4$), were filtered and were concentrated to afford the title intermediate as a pale yellow solid (1.06 g, 89 %). mp 116-117 °C.

29(b) 5-(3-bromophenyl)-3-methyl[1,2,4]thiadiazole

A solution of 3-bromothiobenzamide (0.94 g, 4.37 mmol) in dimethylacetamide dimethylacetal (15 mL) was stirred for 1 h at room temperature under an argon atmosphere, then was evaporated and was redissolved in ethanol (10 mL). After rapid addition of pyridine (0.72 mL) and a solution of hydroxylamine-O-sulfonic acid (0.54 g, 4.81 mmol) in methanol (6.5 mL), the solution was stirred at room temperature for 3 h, was partially concentrated, was diluted with water and was extracted twice with dichloromethane. The combined extracts were washed with 0.3 N sodium hydroxide and water, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography, eluting with 5:95 ethyl acetate:hexanes, to afford the title intermediate as a very viscous, pale orange oil (0.70 g, 63%). Also isolated was slightly impure intermediate (0.25 g, 22%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.85 (d, J=7.8 Hz, 1H), 7.65 (d, J=7.8 Hz, 1H), 7.37 (t, J=7.8 Hz, 1H), 2.74 (s, 3H).

29(c) 5-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-3-methyl[1,2,4]thiadiazole

A solution of palladium acetate (0.02 g, 0.09 mmol) and bis(1,4-diphenylphosphino)butane (0.42 g, 0.10 mmol) in deoxygenated dimethoxyethane was heated at 45-50 °C for 1 min, then was cooled. After rapid addition of a solution of 5-

(3-bromophenyl)-3-methyl[1,2,4]thiadiazole (0.38 g, 1.5 mmol) in dimethoxyethane (3 mL), a solid mixture of 3-cyclopentyloxy-4-methoxyphenylboronic acid (0.39 g, 1.65 mmol) and sodium bicarbonate (0.42 g, 5.0 mmol), and water (2.5 mL) the vessel was sealed and was heated at 85-90 °C for 4 h, then the mixture was cooled, was diluted with 10% hydrochloric acid, was extracted three times with ether, was dried ($MgSO_4$), was filtered and was concentrated. The crude product was purified by two successive flash chromatographies, eluting with 5:95 and with 1:9 ethyl acetate:hexanes to afford the title product as a gummy solid (0.33 g, 59%). Trituration with ether:hexanes provided a white solid. mp 83-84 °C. Anal. ($C_{21}H_{22}NO_2S$) calcd: C, 68.82; H, 6.05; N, 7.64; found: C, 68.58; H, 6.07; N, 7.55.

Example 30

Preparation of 5-(4-cyano-3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole, Route A

30(a) methyl 2-(2-methoxyethoxymethyl)-5-bromobenzoate

A solution of methyl 2-hydroxy-5-bromobenzoate (2.6 g, 11.3 mmol) in tetrahydrofuran (10 mL) was added dropwise over 15 min to a suspension of 80% sodium hydride in mineral oil (0.38 g, 12.4 mmol) suspended in tetrahydrofuran (40 mL) at 0 °C under an argon atmosphere and was stirred for 30 min. 2-Methoxyethoxymethyl chloride (1.55 mL, 13.6 mmol) was added over 5 min and the reaction was stirred at room temperature for 6 h, quenched with ammonium chloride, was extracted three times with dichloromethane, was dried ($MgSO_4$), was filtered and was concentrated. The crude mixture was purified by flash chromatography, eluting with 3:7 ethyl acetate:hexanes to afford the title intermediate as a colorless liquid (2.46 g, 68%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J=2.7 Hz, 1H), 7.53 (dd, J=8.8, 2.7 Hz, 1H), 7.16 (d, J=8.8 Hz, 1H), 5.32 (s, 2H), 3.88 (s, 3H), 3.86 (m, 2H), 3.55 (m, 2H), 3.36 (s, 3H).

30(b) 2-(2-methoxyethoxymethyl)-5-bromobenzamide

A mixture of methyl 2-(2-methoxyethoxymethyl)-5-bromobenzoate (0.96 g, 3 mmol) and several crystals of sodium cyanide (catalytic) in liquid ammonia (~3 mL) was heated in a sealed pressure vessel at 45-50 °C for 48 h, cooled, concentrated, diluted with an aqueous solution of potassium carbonate, extracted with 5:95 methanol:dichloromethane, dried ($MgSO_4$), filtered, and concentrated to provide the title intermediate as a colorless oil (0.83 g, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J=2.6 Hz, 1H), 7.65 (br, 1H), 7.54 (dd, J=8.8, 2.6 Hz, 1H), 7.14 (d, J=8.8 Hz, 1H), 6.70 (br, 1H), 5.42 (s, 2H), 3.86 (m, 2H), 3.50 (m, 2H), 3.37 (s, 3H).

30(c) 5-(1-(2-methoxyethoxymethyl)-4-bromophenyl-2-yl)-3-methyl[1,2,4]oxadiazole

2-(2-methoxyethoxymethyl)-5-bromobenzamide (0.83 g, 2.72 mmol) was dissolved in dimethylacetamide dimethylacetal (4 mL), stirred at 100 °C for 1 h, then concentrated. A solution of this residue in 1,4-dioxane (5 mL) and acetic acid (5 mL) was treated with

hydroxylamine hydrochloride (0.29 g, 4.2 mmol) and a solution of sodium hydroxide (0.18 g, 4.5 mmol) in water (1 mL), stirred at 90-95 °C for 1 h, cooled, diluted with water, extracted three times with dichloromethane, dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by flash chromatography, eluting with 3:7 ethyl acetate:hexanes to afford the title intermediate (0.75 g, 80%), as a white solid. mp 80-81 °C.

30(d) 5-(1-hydroxy-4-bromophenyl-2-yl)-3-methyl[1,2,4]oxadiazole

A solution of 5-(1-(2-methoxyethoxymethyl)-4-bromophenyl-2-yl)-3-methyl[1,2,4]oxadiazole (0.72 g, 1.4 mmol) and trifluoromethanesulfonic acid (1.5 mL, 16.9 mmol) in dichloromethane (10 mL) was stirred at room temperature under an argon atmosphere for 8 h, quenched with aqueous sodium bicarbonate solution, extracted twice with dichloromethane, dried ($MgSO_4$), filtered, and concentrated. The crude mixture was combined with a previous run (0.94 g) and purified by flash chromatography, eluting with 5:95 ethyl acetate:hexanes to afford the title intermediate as a white solid (0.47 g, 100%). mp 83-84 °C.

30(e) 5-(3'-cyclopentyloxy-4'-methoxy-4-hydroxy[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole

Following the procedure of Example 29(c), except substituting 5-(1-hydroxy-4-bromophenyl-2-yl)-3-methyl[1,2,4]oxadiazole for 5-(3-bromophenyl)-3-methyl[1,2,4]thiadiazole the title intermediate was prepared as a pale yellow gum (0.21 g, 32%). ^1H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.08 (d, J=2.3 Hz, 1H), 7.69 (d, J=8.6 Hz, 1H), 7.16 (dd, J=8.4, 2.1 Hz, 1H), 7.17 (d, J=8.6 Hz, 1H), 7.11 (dd, J=8.1, 1.8 Hz, 2H), 6.95 (d, J=8.1 Hz, 1H), 4.88 (m, 1H), 3.90 (s, 3H), 2.52 (s, 3H), 1.8-2.0 (m, 6H), 1.6-1.7 (m, 2H).

30(f) 5-(3'-cyclopentyloxy-4'-methoxy-4-trifluoromethylsulfonato[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole

Following the procedure of Example 8(c), except substituting 5-(3'-cyclopentyloxy-4'-methoxy-4-hydroxy[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole for methyl 3'-cyclopentyloxy-4'-methoxy-4-hydroxy[1,1']biphenyl-3-carboxylate the title intermediate was prepared as a colorless oil (0.18 g, 65%). ^1H NMR (400 MHz, $CDCl_3$) d 8.33 (d, J=2.4 Hz, 1H), 7.79 (dd, J=8.6, 2.4 Hz, 1H), 7.50 (d, J=8.6 Hz, 1H), 7.16 (dd, J=8.4, 2.1 Hz, 1H), 7.11 (d, J=2.1 Hz, 1H), 6.97 (d, J=8.4 Hz, 1H), 4.88 (m, 1H), 3.90 (s, 3H), 2.50 (s, 3H), 1.8-2.0 (m, 6H), 1.6-1.7 (m, 2H).

30(g) 5-(3'-cyclopentyloxy-4'-methoxy-4-cyano[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole

Following the procedure of Example 8(d), except substituting 5-(3'-cyclopentyloxy-4'-methoxy-4-trifluoromethylsulfonato[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole for

methyl 3'-cyclopentyloxy-4'-methoxy-4-trifluoromethylsulfonato[1,1']biphenyl-3-carboxylate the title product was prepared as a white solid (0.013 g, 13%). mp 130-132 °C.

Example 31

Preparation of 5-(4-cyano-3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole, Route B

31(a) 5-bromo-2-carbomethoxybenzamide

A solution of 4-bromophthalic acid (5 g, 20.5 mmol), sulfuric acid (5 mL), and methanol (100 mL) was refluxed for 24 h, cooled, neutralized with sodium bicarbonate, concentrated, diluted with dichloromethane, and extracted three times with 10% sodium hydroxide. The aqueous phase was acidified, extracted with 1:9 methanol:dichloromethane, dried ($MgSO_4$), filtered, and concentrated to provide a 1:1 mixture of acids. A solution of this mixture (4.36 g, 17.4 mmol) and N-methylmorpholine (2.1 mL, 19.2 mmol) in dimethoxyethane (70 mL) was treated dropwise with isobutylchloroformate (2.40 mL, 18.3 mmol), stirred 7 min, then treated with concentrated ammonium hydroxide (5 mL) and stirred for 1.5 h. The mixture was acidified, extracted three times with 1:9 methanol:dichloromethane, dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by flash chromatography, eluting with 7:3 ethyl acetate:hexanes to afford the title intermediate as a white solid (0.90 g, 17%). mp 126-128 °C.

31(b) 5-(5-bromo-2-carbomethoxyphenyl)-3-methyl[1,2,4]oxadiazole

Following the procedure of Example 8c, except substituting 2-carbomethoxy-5-bromobenzamide for 2-(2-methoxyethoxymethyl)-5-bromobenzamide the title intermediate was prepared as a colorless oil (0.08 g, 27%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.78 (s, 2H), 3.85 (s, 3H), 2.50 (s, 3H).

31(c) 5-(2-carboxamido-5-bromophenyl)-3-methyl[1,2,4]oxadiazole

A solution of 5-(2-carbomethoxy-5-bromophenyl)-3-methyl[1,2,4]oxadiazole (0.076 g, 0.25 mmol) and potassium hydroxide (0.016 g, 0.28 mmol) in tetrahydrofuran (1.25 mL), methanol (1.25 mL), and water (0.5 mL) was stirred at room temperature for 24 h, acidified with 10% hydrochloric acid, extracted three times with 5:95 methanol:dichloromethane, dried ($MgSO_4$), filtered, and concentrated. The residue and N-methylmorpholine (0.03 mL, 0.28 mmol) in dimethoxyethane (1.5 mL) at room temperature under an argon atmosphere was treated dropwise with isobutylchloroformate (0.034 mL, 0.26 mmol), stirred 5 min, then treated with concentrated ammonium hydroxide (3 drops) and stirred for 1 h. The mixture was diluted with water, extracted three times with 5:95 methanol:dichloromethane, dried ($MgSO_4$), filtered, and concentrated to afford the title intermediate as a white solid (0.056 g, 79%). mp 195-198 °C.

31(d) 5-(2-cyano-5-bromophenyl)-3-methyl[1,2,4]oxadiazole

A solution of 5-(2-carboxamido-5-bromophenyl)-3-methyl[1,2,4]oxadiazole (0.05 g, 0.18 mmol), pyridine (0.032 mL, 0.39 mmol), and trifluoroacetic anhydride (0.03 mL, 0.20 mmol) in tetrahydrofuran (2 mL) was stirred at room temperature under argon for 5 h. Pyridine (0.032 mL, 0.039 mmol) and trifluoroacetic anhydride (0.03 mL, 0.20 mmol) was added, and stirring continued for 1 h. The mixture was diluted with ether, washed twice with 10% hydrochloric acid, water, and brine, dried ($MgSO_4$), filtered, and concentrated to afford the title intermediate as an oil (0.046 g, 96%). ^1H NMR (400 MHz, $CDCl_3$) d 8.40 (s, 1H), 7.84 (d, J=8.2Hz, 1H), 7.75 (d, J=8.2 Hz, 1H), 2.54 (s, 3H).

31(e) 5-(3'-cyclopentyloxy-4'-methoxy-4-cyano[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole

Following the procedure of Example 29(c), except substituting 5-(2-cyano-5-bromophenyl)-3-methyl[1,2,4]oxadiazole for 5-(3-bromophenyl)-3-methyl[1,2,4]thiadiazole the title product was prepared (0.038 g, 68%), then further triturated from dichloromethane:hexanes to provide a white solid. mp 132-134 °C. Anal. ($C_{22}H_{21}N_3O_3 \cdot 0.25\ H_2O$) calcd: C, 69.55; H, 5.70; N, 11.06, found: C, 69.30; H, 5.58; N, 10.94.

Example 32

Preparation of 5-(3'-cyclopentyloxy-2,6-difluoro-4'-methoxy[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole

32(a) 5-(2,4-difluoro-3-iodophenyl-3-yl)-3-methyl[1,2,4]oxadiazole

A solution of 2,4-difluoro-3-iodobenzoic acid (0.54 g, 1.9 mmol), and N-methylmorpholine (0.23 mL, 2.1 mmol) in dimethoxyethane at room temperature under an argon atmosphere was treated dropwise with isobutylchloroformate (0.26 mL, 2.0 mmol). After 5 min conc. ammonium hydroxide (7 drops) was added and stirring continued for 1 h. The reaction was acidified with 10% hydrochloric acid, extracted three times with 5:95 methanol:methylene chloride, dried ($MgSO_4$), and concentrated. The residue was dissolved in dimethylacetamide dimethylacetal (3 mL), stirred at 90-95 °C for 1 h, then concentrated. A solution of this residue in 1,4-dioxane (4 mL) and acetic acid (4 mL) was treated with hydroxylamine hydrochloride (0.18 g, 2.66 mmol) and a solution of sodium hydroxide (0.11 g, 2.85 mmol) in water (1 mL), stirred at 90-95 °C for 1 h, cooled, diluted with water, extracted three times with dichloromethane, dried ($MgSO_4$), filtered, and concentrated. The crude mixture was purified by flash chromatography, eluting with 1:9 ethyl acetate:hexanes to afford the title intermediate as a white solid (0.22 g, 36%). mp 131-133 °C.

32(b) 5-(3'-cyclopentyloxy-4'-methoxy-2,6-difluoro[1,1']biphenyl-3-yl)-3-methyl[1,2,4]oxadiazole

Following the procedure of Example 29(c), except substituting 5-(2,4-difluoro-3-iodophenyl-3-yl)-3-methyl[1,2,4]oxadiazole for 5-(3-bromophenyl)-3-methyl[1,2,4]thiadiazole, the title compound was prepared as a white solid. mp 101-102

°C. Anal. ($C_{21}H_{20}F_2N_2O_3 \cdot 0.375\ H_2O$) calcd: C, 64.15; H, 5.32; N, 7.13; found: C, 64.19; H, 5.26; N, 6.89.

METHODS OF TREATMENT

The compounds of Formula (I), or a pharmaceutically acceptable salt thereof, can be used as discussed above in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human or other mammal which is mediated by inhibition of PDE IV, such as, but not limited to, asthma, allergic, or inflammatory diseases. The compounds of Formula (I) are administered in an amount sufficient to treat such a disease in a human or other mammal.

In order to use a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition using appropriate pharmaceutically acceptable excipients, such as carriers and diluents.

The amount of a compound of Formula (I) required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the condition and the animal undergoing treatment, and is ultimately at the discretion of the physician.

The daily dosage regimen for oral administration is suitably about 0.001 mg/kg to 100 mg/kg, preferably 0.01 mg/kg to 40 mg/kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid or base, whichever is appropriate. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit activity. Administration by inhalation is preferred for treatment of asthma conditions.

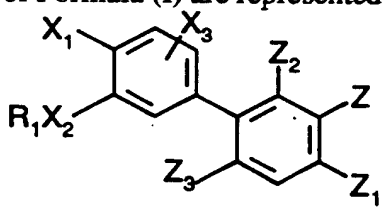
No unacceptable toxic effects are expected when these compounds are administered in accordance with the present invention. Compounds of this invention were found to have useful activity as per the utility examples below.

UTILITY EXAMPLES

The utility of these compounds can be determined using the assays described in prior published patent applications. For example see /PCT/US93/01991 published as WO93/19749. That application is incorporated herein by reference in so far as its disclosure is useful for preparing and running assays which prove the putative utility of these compounds.

What is claimed is:

1. A compound of Formula (I) are represented by the following structure:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is $-(CR_4R_5)_nC(=O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(=O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$ or $-(CR_4R_5)_rR_6$, wherein any alkyl moiety may be optionally substituted with one or more halogens;

R_2 is independently methyl or ethyl, where either methyl or ethyl may be optionally substituted by 1 or more halogens;

each R_4 and each R_5 are independently -H or a C_{1-2} alkyl;

R_6 is -H, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups, one ethyl group or an hydroxyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2: or

b) when R_6 is hydroxyl or -H, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl,or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

each R_7 is independently $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three groups selected from -F, -Br, -Cl, $-NO_2$, $-NR_{10}R_{11}$, $-C(=O)R_8$, $-C(=O)OR_8$, $-OR_8$, -CN, $-C(=O)NR_{10}R_{11}$, $-OC(=O)NR_{10}R_{11}$, $-OC(=O)R_8$, $-NR_{10}C(=O)NR_{10}R_{11}$, $-NR_{10}C(=O)R_{11}$, $-NR_{10}C(=O)OR_9$, $-NR_{10}C(=O)R_{13}$, $-C(=NR_{10})NR_{10}R_{11}$, $-C(=N\text{-}CN)NR_{10}R_{11}$, $-C(=N\text{-}CN)SR_9$, $-NR_{10}C(=N\text{-}CN)NR_{10}R_{11}$, $-NR_{10}S(=O)_2R_9$, $-S(=O)_{m'}R_9$, $-NR_{10}C(=O)C(=O)NR_{10}R_{11}$, $-NR_{10}C(=O)C(=O)R_{10}$, or R_{13};

each R_8 is independently -H or R_9;

each R_9 is independently C_{1-4} alkyl optionally substituted by one to three -F;

each R_{10} is independently $-OR_8$ or R_{11};

each R_{11} is independently -H or C_{1-4} alkyl optionally substituted by one to three -F; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

each R_{12} is independently C_{3-7} cycloalkyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazolyl, 1-imidazolyl, 2-imidazolyl, thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, 2-thienyl, 3-thienyl, 4-thiazolyl, 5-thiazolyl, quinolinyl, naphthyl or phenyl;

each R_{13} is a heterocyclic ring independently selected from oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl or thiadiazolyl, where R_{13} is appended to a compound of Formula (I) through a carbon atom of the heterocyclic ring, and where each heterocyclic ring may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

each R_{14} is independently H or R_7, or when R_{10} and R_{14} are as $NR_{10}R_{14}$, they may together with the nitrogen atom form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

each m is independently 0 to 2;

each m' is independently 0 to 2;

n is 1 to 4;

r is 0 to 6;

each q is independently 0 to 2.

X_1 is YR_6, halogen, nitro, NR_4R_5 or formyl amino;

X_2 is O or NR_8;

X_3 is hydrogen or X_1;

Y is O or $S(=O)_{m'}$;

Y' is O or S;

Z, Z_2 and Z_3 are independently H, $(CH_2)_{1-3}CN$, $(CH_2)_{1-3}(C=O)OR_{14}$, $C(=O)H$, $C(=NR_{10})NR_{10}R_{14}$, $C(=NOR_8)R_{14}$, $C(=O)NR_8NR_8C(=O)R_8$, $C(=O)NR_8NR_{10}R_{14}$, $C(=NOR_{14})R_8$, $C(=NR_8)NR_{10}R_{14}$, $C(=NR_{14})NR_8R_8$, $C(=N\text{-}CN)NR_{10}R_{14}$, $C(=N\text{-}CN)SR_9$, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 4-triazolyl[1,2,3], 5-triazolyl[1,2,3], 3-triazolyl[1,2,4], 5-triazolyl[1,2,4], 5-tetrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-oxadiazolyl[1,2,4], 5-oxadiazolyl[1,2,4], 2-oxadiazolyl[1,3,4], 2-thiadiazolyl[1,3,4], 5-thiadiazolyl[1,2,4], 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolidinyl, 4-oxazolidinyl, 5-oxazolidinyl, 2-thiazolidinyl, 4-thiazolidinyl or 5-thiazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, or 5-

imidazolidinyl; wherein all of the heterocyclic ring systems may be optionally substituted one or more times by R_{14}; and

Z_1 is H, OH, CN, C(=O)OH, C(=O)OCH_3 OR C(=O)NH_2;

with the provisos that:

a) at least one of Z, Z_2 and Z_3 is other than H;

b) at least one of Z, Z_2 and Z_3 is H;

c) when Z_1 is -C(=O)OH, then X_2R_1 is not methoxy; and

d) when Z_2 is $(CH_2)_{1-3}CN$, or $(CH_2)_{1-3}C(C=)OR_{14}$, then Z_3 is H.

2. A compound of claim 1 wherein Z is oxadiazole, thiadiazole, tetrazole, carboxyaldehyde, or acetonitrile, or Z_2 is oxadiazole, acetonitrile or tetrazole

3. A compound of claim 2 which is

3-(3'-cyclopentyloxy-4'methoxy[1,1']biphenyl-3yl)-5-methyl[1,2,4]oxadiazole;

5-(3'-cyclopentyloxy-4'methoxy[1,1']biphenyl-3yl)-3-methyl[1,2,4]oxadiazole;

5-(3'-cyclopentyloxy-2,6-difluoro-4'methoxy[1,1']biphenyl-3yl)-3-methyl[1,2,4]oxadiazole;

5-(4-cyano-3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-3-methyl[1,2,4]oxadiazole;

2-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-5-methyl[1,3,4]oxadiazole;

2-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-5-methyl[1,3,4]thiadiazole;

5-(3'-cyclopentyloxy-4'-methoxy[1,1']biphenyl-3yl)-3-methyl[1,2,4]thiadiazole;

5-(3'-cyclopentyloxy-4'methoxy[1,1']biphenyl-3yl)-1-methyl-1H-tetrazole;

5-(3'-cyclopentyloxy-4'methoxy[1,1']biphenyl-3yl)-2-methyl-2H-tetrazole;

3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-3-acetonitrile;

3'-cyclopropylmethoxy-4'-methoxy[1,1']biphenyl-2-acetonitrile; or

3'-cyclopropylmethoxy-4-hydroxy-4'-methoxy[1,1']biphenyl-3-carboxaldehyde, or a pharmaceutically acceptable salt of any compound which can form such a salt.

4. A pharmaceutical composition comprising a compound of Formula (I) according to claim 1 and a pharmaceutically acceptable excipient.

5. A method for treating an allergic or inflammatory state which method comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) according to claim 1 alone or in combination with a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04294

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	CHEMICAL ABSTRACTS, VOLUME 121, NO. 21, ISSUED 21 NOVEMBER 1994, DUPLANTIER ET AL, "CATECHOL DIETHERS AS SELECTIVE PHOSPHODIESTERASE INIBITORS," SEE ENTIRE ABSRACT, ABSTRACT NO.255405V,PCT INT. APPL. WO 94 12,461,09 JUNE 1994, US APPL. 984408 02 DECEMBER 1992.	1-5
X,P	CHEMICAL ABSTRACTS,VOLUME 122, NO. 3, ISSUED 16 JANUARY 1994, BOYD ET. AL., "TRI-SUBSTITUTED PHENYL DERIVATIVES AS PHOSPHODIESTERASE INHIBITORS AND PROCESSES FOR THEIR PREPARATION," SEE ENTIRE ABSTRACT, ABSTRACT NO. 31544X, PCT INT. APPL. WO94 10,118, 11 MAY 1994, GB APPL. 92/22253, 23 OCTOBER 1992 .	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 13 JULY 1995	Date of mailing of the international search report 26 JUL 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ROBERT GERSTL Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04294

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07C 43/23, 47/575, 65/24, 69/94, 69/712, 235/42, 255/37, 255/54, 255/57; C07D 257/04, 271/06, 271/10, 285/08 285/10, ; A61K 31/09, 31/11, 31/165, 31/195, 31/235, 31/275, 31/41

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/361,363,364,381,521,522,525,530,531,568,622; 548/128,131,143,136,252; 558/406, 410, 423; 560/59;562/469;564/171

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/361,363,364,381,521,522,525,530,531,568,622; 548/128,131,143,136,252; 558/406, 410, 423; 560/59;562/469;564/171